REMARKS/ARGUMENTS

Claims 1-19 have been canceled without prejudice to or disclaimer of the subject matter encompassed thereby in order to further prosecution of this application. Applicants expressly reserve the right to file continuing applications or take other such appropriate measures to seek protection of the inventions encompassed by the canceled subject matter. Claims 20-44 have been added. Support for these new claims can be found throughout the specification, and in the original claims, as described below. Therefore, no new matter has been added by presentation of new claims. Entry of these claims into the above-identified application is respectfully requested.

New claims 20-44 are drawn to methods of treating non-Hodgkin's B-cell lymphoma, comprising administering at least one therapeutically effective dose of an anti-CD20 antibody or fragment thereof in combination with administration of at least one therapeutically effective dose of interleukin-2 (IL-2) or biologically active variant thereof, wherein the therapeutically effective dose of the anti-CD20 antibody or fragment thereof is in the range from about 125 mg/m^2 to about 500 mg/m^2 and the therapeutically effective dose of IL-2 or variant thereof is in the range from about 1 mIU/m^2 to about 14 mIU/m^2. Support for new claim 20 may be found in original claims 1, 2, 4, and 13. Support for the recited dose of IL-2 may be found in the specification, for example, on page 11, lines 21-23. Support for biologically active variants may be found, for example, on page 14, line 18, continuing through page 15, line 2. Support for new claim 21 may be found in original claim 13. Support for new claims 22 and 34 may be found in original claim 14. Support for new claims 23 and 35 may be found in original claim 15. Support for new claims 24 and 38 may be found in the original claims and throughout the specification, for example, on page 11, lines 21-25, and page 12, lines 1-3. Support for new claims 25 and 39 may be found in original claim 5. Support for new claims 26 and 40 may be found in original claims 4 and 8. Support for new claims 27 and 41 may be found in original claims 9 and 10. Support for new claims 28 and 42 may be found throughout the specification, for example, on page 19, lines 6-8. Support for new claims 29 and 43 may be found in original claim 6, and throughout the specification, for example, on page 14, lines 19-21. Support for new claims 30 and 44 may be found in original claim 7, and throughout the specification, for example, on page 14, lines 19-21. Support for new claim 31 may be found in original claim 16. Support for new claims 32 and

36 may be found in original claim 18. Support for new claims 33 and 37 may be found throughout the specification, for example, on page 29, line 31, continuing through page 30, line 2.

Claims 20-44 are now pending in the application. Reexamination and reconsideration of the claims are respectfully requested in view of these amendments and the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C. §102(a) Should Be Withdrawn

Claims 1-7, 13-15, and 17 are rejected under 35 U.S.C. §102(a) as being anticipated by Freidberg *et al.* (*Blood* (11/16/00) Vol. 96(11), part 1, p. 730a). Claims 1-7, 13-15, and 17 have been canceled to further prosecution. This rejection is respectfully traversed as applied to any overlapping subject matter now recited in new claims 20-44.

Applicants respectfully request that the claim for priority under 35 U.S.C. §119(e) be granted to U.S. Provisional Application No. 60/192,047, which has a filing date of March 24, 2000. The subject matter recited in original claims 1-19, as well as the subject matter recited in new claims 20-44, is fully supported by this provisional application. If the Examiner is still unable to access the file for this provisional application, Applicants will supply a copy of the application as filed on March 24, 2000, upon request.

As Applicants' priority document predates the publication date for the Freidberg *et al.* reference, this rejection of the claims under 35 U.S.C. §102(a) is improper and should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 1-7 and 13-16 are rejected under 35 U.S.C. §102(b) as being anticipated by Yirinec *et al.* (*Blood* (11/15/99) Vol. 94, p. 270b, Abstract #4420). Claims 1-7 and 13-16 have been canceled to further prosecution. This rejection is respectfully traversed as applied to any overlapping subject matter now recited in new claims 20-44.

Applicants respectfully request that the claim for priority under 35 U.S.C. §119(e) be granted to U.S. Provisional Application No. 60/192,047, which has a filing date of March 24, 2000. As noted above, the subject matter recited in original claims 1-19, as well as the subject matter recited in new claims 20-44, is fully supported by this provisional application. In view of this, this rejection is improper, as the Yirinec *et al.* abstract published less than one year before the earliest effective filing date of the present application. Accordingly, this rejection should be withdrawn.

As the proper claim for priority resides in U.S. Provisional Application No. 60/192,047, which has a filing date of March 24, 2000, the Yirinec *et al.* reference could be construed as prior art under 35 U.S.C. §102(a). Though the subject matter recited in new claims 20-44 has not been rejected under §102(a) in view of this cited reference, Yirinec *et al.* has been cited as the basis of a §103 rejection with respect to overlapping subject matter originally recited in the rejected claims. Applicants respectfully submit that the Yirinec *et al.* reference cannot properly be used as prior art under §102(a) or §103 for the following reasons.

As discussed in MPEP 2132.01 (citing *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982)),

> Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). . . . The rejection can be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work.

As indicated on page 1 of the specification, the present application claims the benefit of U.S Provisional Application No. 60/192,047, filed March 24, 2000. The Yirinec *et al.* abstract has a publication date of November 11, 1999, which is less than one year before the effective filing date of the instant application. Furthermore, Applicants submit concurrently herewith a specific declaration by Applicant Joseph D. Rosenblatt, co-inventor on this application, which establishes that the Yirinec *et al.* article is describing Applicants' own work. The additional nine co-authors listed on this abstract served as technical assistants, working under the direction and instructions of Applicant Rosenblatt. Accordingly, it would be improper to reject original claims 1-7 and 13-16, and overlapping subject matter now recited in new claims 20-44, under 35 U.S.C. §102(a) as

being anticipated by Yirinic *et al.*, and similarly improper to reject the original and newly presented claims as being obvious in view of Applicants' own work

In view of these remarks and the submission of Applicant Rosenblatt's declaration, Applicants respectfully submit that this rejection should be withdrawn and should not be applied to new claims 20-44.

Claims 1, 3, and 4 are rejected under 35 U.S.C. §102(b) as being anticipated by Hooijberg *et al.* (*Cancer Research* (1995) Vol. 55, p. 2627). Claims 1, 3, and 4 have been canceled to further prosecution. New claims 20-44 recite methods that were not subject to this rejection. Accordingly, this rejection should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Friedberg *et al.* (*Blood* (11/16/00) Vol. 96(11), part 1, p. 730a) in view of Applicants' admission on page 18, line 11, continuing through page 21, where variants of IL-2 known in the art are disclosed. Claims 1-19 have been canceled to further prosecution. This rejection is respectfully traversed as applied to any overlapping subject matter now recited in new claims 20-44.

Applicants respectfully request that the claim for priority under 35 U.S.C. §119(e) be granted to U.S. Provisional Application No. 60/192,047, which has a filing date of March 24, 2000. As noted above, the subject matter recited in original claims 1-19, as well as the subject matter recited in new claims 20-44, is fully supported by this provisional application. As Applicants' priority document predates the publication date for the Freidberg *et al.* reference, this rejection of the claims under 35 U.S.C. §103(a) is improper and should be withdrawn.

Claims 1-19 are rejected under 35 U.S.C. §103(a) as being obvious over Yirinec *et al.* (*Blood* Vol. 94, p. 270b, Abstract #4420), in view of Applicants' admission on page 18, line 11, continuing through page 21, where variants of IL-2 known in the art are disclosed. Claims 1-19 have been canceled to further prosecution. This rejection is respectfully traversed as applied to any overlapping subject matter now recited in new claims 20-44.

Applicants submit concurrently herewith a specific declaration by Applicant Joseph D. Rosenblatt, co-inventor on this application, which establishes that the Yirinec *et al.* article is describing Applicants' own work. As noted above, the additional nine co-authors listed on this abstract served as technical assistants, working under the direction and instructions of Applicant Rosenblatt. Accordingly, it would be improper to reject original claims 1-19, and overlapping subject matter now recited in new claims 20-44, under 35 U.S.C. §103(a) as being obvious in view of Yirinic *et al.*, which describes Applicants' own work.

In view of these remarks and the submission of Applicant Rosenblatt's declaration, Applicants respectfully submit that this rejection should be withdrawn and should not be applied to new claims 20-44.

Claims 1, 3-5, and 7-19 are rejected under 35 U.S.C. §103(a) as being obvious over Hooijberg *et al.* (*Cancer Research* (1995) Vol. 55, p. 2627) in view of Applicants' admission on page 4, line 13, and page 18, line 11, continuing through page 21. Claims 1, 3-5, and 7-19 have been canceled. This rejection is respectfully traversed as applied to any overlapping subject matter now recited in claims new claims 20-44.

New claims 20-23, 25-27, 29-32, 34-36, 39-41, 43, and 44 encompass subject matter set forth in original claims 1, 3-5, and 7-19. Applicants respectfully submit that the newly claimed subject matter is not taught or suggested by the cited reference for reasons noted below. Accordingly, this rejection under 35 U.S.C. §103(a) should not be applied to the newly submitted claims.

Hooijberg *et al.* disclose the treatment of B cell cancers in a murine model using a combination of anti-CD20 antibodies and rhIL-2. However, as stated in the current application,

> "[t]he IL-2 was given weekly and in a subcutaneous dose of 200,000 units/mouse. The equivalent dose in humans could be as high as 6×10^8 IU, which is a large, essentially unwieldy dose that is greater than high-dose bolus used in treatment of renal cell carcinoma or metastatic melanoma."

To establish a *prima facie* case of obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143, citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). It is Applicants' contention that a *prima facie* case of obviousness has not been established for the rejection set forth above.

The Examiner states that it is within the purview of one skilled in the art to optimize treatment conditions. See the Office Action mailed October 2, 2004, at page 7, paragraph 1. However, Applicants contend that there is no guidance whatsoever in Hooijberg *et al.* as to a dosage range of IL-2 that would be effective for treating non-Hodgkin's B-cell lymphoma in a human when administered in combination with an anti-CD20 antibody. In contrast, Applicants' claimed invention recites a dose of about 1 mIU/m^2 to about 14 mIU/m^2 to be administered in combination with the recited dose of anti-CD20 antibody. As Applicants have noted in the current application and cited to herein above, the IL-2 dose disclosed in Hooijberg *et al.* is weekly subcutaneous administration of 200,000 units IL-2/mouse. The equivalent dose in a human is as high as 6 x 10^8 IU, which falls well outside the claimed IL-2 dosing range for a human, i.e., about 1 mIU/m^2 to about 14 mIU/m^2. Therefore, Applicants contend that the cited prior art either teaches a specific combination of IL-2/antibody dosing ranges that teaches away from the presently claimed invention, or generically suggests treatment of B cell cancers with a combination of IL-2 and monoclonal antibody. The teachings of the latter represent an invitation to experiment; yet an invitation to experiment is not sufficient grounds to reject an invention as obvious.

Judge Rich explains in *In re Tomlinson* : "[t]here is usually an element of 'obviousness to try' in any research endeavor, that it is not undertaken with complete blindness, but with some semblance of a chance of success, and that patentability determinations [of obviousness] based on that as a test would not only be contrary to statute but result in a marked deterioration of the patent system as an incentive to invest in those efforts and attempts which go by the name of research." *In re Tomlinson* 363 F.2d 928, 931 (CCPA 1966). Under the Examiner's theory,

conducting experiments with the possibility of success renders inventions obvious, if the experiment is actually successful; however, no court has applied this standard. By asserting that the present invention would be successful in light of the teachings of the Hooijberg *et al.* reference, the Examiner has used impermissible hindsight.

Furthermore, "Applicants' admission" referred to by the Examiner is drawn to statements that disclose the prior art knowledge of the existence of the IDEC-C2B8 antibody and IL-2 variants. The fact that the IDEC-C2B8 antibody was known to exist, and that variants of IL-2 were known in the art, does not provide any suggestion as to what doses of anti-CD20 antibody or fragment thereof and IL-2 or variant thereof should be used in combination to treat human subjects with non-Hodgkin's B-cell lymphoma. That missing information is not taught or suggested in the cited Hooijberg *et al.* reference.

In view of these remarks, Applicants respectfully submit that the cited reference alone or in combination with "Applicants' admission" does not teach or even suggest all of the claim limitations, nor does it provide to one of skill in the art a reasonable expectation of successfully modifying the teachings of this reference to arrive at Applicants' claimed invention. As such, a *prima facie* case of obviousness has not been established, and this rejection of the claims should be withdrawn and should not be applied to new claims 20-44.

Claims 1-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 00/09160 or U.S. Patent No. 6,455,043, in view of Applicants' admission on page 18, line 11, continuing through page 21, where variants of IL-2 known in the art are disclosed. Claims 1-19 have been canceled to further prosecution. This rejection is respectfully traversed as applied to any overlapping subject matter now recited in new claims 20-44.

New claims 20-23, 25-27, 29-32, 34-36, 39-41, 43, and 44 encompass subject matter set forth in original claims 1-19. Applicants submit that the claimed invention is not taught or suggested by the cited references for reasons noted below. Accordingly, this rejection under 35 U.S.C. §103 should not be applied to the newly submitted claims.

WO 00/09160 is the PCT application corresponding to U.S. Patent No. 6,455,043. These references both disclose combined therapeutic regimens for non-Hodgkin's B cell lymphomas

using anti-CD20 antibodies and cytokines, radiotherapy, myeloablative therapy, or chemotherapy. The use of IL-2 in combination with Rituximab® is suggested; however, these references fail to disclose the claimed dose of IL-2 that is to be used in combination with Rituximab® or any other anti-CD20 antibody.

The Examiner states that it is within the purview of one skilled in the art to optimize treatment conditions and dosages (Office Action mailed October 2, 2003, at page 8, paragraph 3), thus rendering obvious the claimed invention. Applicants respectfully disagree.

Applicants note that both IL-2 and Rituximab individually can produce undesirable side effects. See the package inserts for the commercially available Rituxan® (i.e., Rituximab) and the commercially available IL-2 product, Proleukin®, copies of which are readily available on the internet. It is true that the undesirable side effects of these drugs have been minimized with respect to their individual FDA-approved clinical uses, but reduction of these unwanted side effects without compromising therapeutic efficacy of these drugs was achieved because clinical trials were carried out in humans to determine what dose of the individual drug would be both efficacious and tolerated by human subjects. However, it cannot be said that the fact that clinical trials were required to find out what dose would be both efficacious and tolerable, these trials then rendered obvious the efficacious and tolerable dose for either of these drugs.

Where combination therapy with two drugs is undertaken, one cannot predict what the combined effect of the two drugs will be, particularly where the two drugs individually have known undesirable side effects. As a result, it becomes all the more difficult to predict with a reasonable expectation of success what will be the efficacious and tolerable dose for each drug. Accordingly, the mere suggestion in the WO 00/09160 or U.S. Patent No. 6,455,043 reference that two drugs should be used together does not render obvious to one of skill in the art what doses would be both therapeutically effective and tolerable when these two drugs are administered in combination. Again, this suggestion merely represents an invitation to experiment; yet an invitation to experiment is not sufficient grounds to reject an invention as obvious for reasons outlined herein above.

Applicants respectfully submit that the optimization of treatment conditions, such as determining dosage amounts and/or frequency of dosing, is not necessarily routine, particularly

where combination therapy is involved. In the present case, there is no suggestion in these two cited prior art references of a dose range for IL-2 that is to be administered in combination with an anti-CD20 antibody that would be both tolerable and efficacious in treating non-Hodgkin's B-cell lymphoma, much less a suggestion of the particular therapeutically effective doses recited in Applicants' claimed invention. Applicants are the first to discover what doses of these two therapeutic agents should be used in combination therapy for non-Hodgkin's B-cell lymphomas, and have further shown efficacy and tolerability in clinical trials in humans.

Furthermore, the fact that variants of IL-2 were known in the art at the time of Applicants' invention does not provide any suggestion as to what doses of anti-CD20 antibody or fragment thereof and IL-2 or variant thereof should be used in combination to treat human subjects with non-Hodgkin's B-cell lymphomas. That missing information is not taught or suggested in the cited WO 00/09160 and U.S. Patent No. 6,455,043 references.

In view of these remarks, Applicants respectfully submit that these two cited references alone or in combination with "Applicants' admission" do not teach or even suggest all of the claim limitations, nor do they provide to one of skill in the art a reasonable expectation of successfully modifying the teachings of these cited references to arrive at Applicants' claimed invention. As such, a *prima facie* case of obviousness has not been established, and this rejection of the claims should be withdrawn and should not be applied to new claims 20-44.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §§ 102(a), 102(b), and § 103(a) are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper.

However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Lynda-Jo Pixley